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Diabetes: Rethinking risk and the Dx that fits

The USPSTF now calls for screening patients with mild hypertension. A late-onset variant is now in the classification mix. Use these tools and tips to better evaluate patients.

Practice recommendations

- Routinely screen adult patients with a sustained blood pressure >135/80 mm Hg for type 2 diabetes (SOR: **B**).
- Closely monitor pregnant women with 1 or more elevated glucose test results; although a diagnosis of gestational diabetes mellitus (GDM) requires 2 or more abnormal values, even 1 may be associated with a higher risk of adverse outcomes (SOR: **C**).
- Include latent autoimmune diabetes in adults (LADA), a progressive form of type 1 with a slower onset, in the differential diagnosis for symptomatic patients who don't fit the classic patterns for type 1 or type 2 diabetes (SOR: **B**).

Strength of recommendation (SOR)
A Good-quality patient-oriented evidence
B Inconsistent or limited-quality patient-oriented evidence
C Consensus, usual practice, opinion, disease-oriented evidence, case series

The youngest Americans—those born in the year 2000 or thereafter—have more than a 1 in 3 lifetime risk of developing diabetes, according to the Centers for Disease Control and Prevention.[1] That estimate, coupled with the fact that more than 2 out of 3 adults and 1 in 6 children between the ages of 2 and 19 years are overweight,[2] would seem to indicate a need for widespread diabetes screening. But limited health care resources, a lack of evidence that mass screening improves outcomes, and differences among leading medical associations about whom and when to screen argue against it.

At the same time, widespread obesity is making the presentation of hyperglycemia more complex and the forms of diabetes harder to classify. Many cases don't follow the classic patterns, in which type 1 (formerly called juvenile diabetes) virtually always emerges in childhood and type 2 (previously known as adult-onset diabetes) is strictly an adult disease. Our evolving understanding of diabetes has led researchers to focus on prediabetes (defined as impaired fasting glucose, impaired glucose tolerance, or both) and latent autoimmune diabetes in adults (LADA), a recently reported type 1 variant that some have labeled type 1.5.[3]

In the face of growing complexity, the US Preventive Services Task Force (USPSTF) last year upgraded its recommendation for screening for type 2 diabetes, and researchers have developed new

risk calculation tools. We've taken a look at the changing clinical landscape and sorted through the latest evidence to help you make sense of the latest risk and diagnostic developments in diabetes care.

Screening for type 2: A look at guidelines

Type 2 diabetes accounts for approximately 90% of the cases you'll see.[1,4,5] The American Diabetes Association (ADA) calls for routine screening, starting at 45 years of age and continuing every 3 years thereafter in the absence of risk. But for those who are overweight or obese and have 1 or more additional risk factors, screening is recommended at any age.[5] In addition to a body mass index (BMI) ≥25, risks include physical inactivity, a first-degree relative with type 2 diabetes, blood pressure >135/80 mm Hg (or controlled with an antihypertensive), high-density lipoproteins (HDL) <35 mg/dL, triglycerides >250 mg/dL, polycystic ovary syndrome, impaired glucose tolerance or impaired fasting glucose, and acanthosis nigricans, a pigmented thickening of the skin folds of the neck (**TABLE**).[6,7] Patients with the metabolic syndrome—abdominal obesity (defined as a waist circumference of >40" in men and >35" in women) and ≥2 of the following: raised triglyceride levels, elevated blood pressure, elevated fasting plasma glucose, and reduced HDL cholesterol—are at especially high risk of both cardiovascular disease and type 2 diabetes.[8]

The ADA screening recommendations, however, are not based on prospective outcome studies, nor are they widely followed. Until recently, the USPSTF only recommended screening adults with hypertension and hyperlipidemia.

In 2008, after an assessment of new findings and research updates, the USPSTF revised its recommendation: The task force now calls for screening asymptomatic adults with sustained blood pressure >135/80 mm Hg—regardless of lipid profile.[7] For patients with diabetes and hypertension, the USPSTF concluded, evidence shows that early intervention—including lowering blood pressure below conventional targets—can prevent long-term adverse outcomes of diabetes and reduce the risk of cardiovascular events.

Although mass screening remains controversial, regular assessment of risk factors and targeting individuals with established risk is clearly indicated (**PATIENT HANDOUT**). The importance of early detection was highlighted by the United Kingdom Prospective Diabetes Study, in which approximately half of the patients with newly diagnosed type 2 diabetes already had evidence of complications.[9]

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The USPSTF recommends screening asymptomatic adults whose blood pressure is >135/80 mm Hg for type 2 diabetes, regardless of lipid profile.

Validated risk calculators can boost detection rates

In an attempt to improve detection rates of type 2 diabetes and prediabetes, researchers in both the United States and the United Kingdom recently developed easy-to-use risk calculation tools. The **Diabetes Risk Calculator** (available at

http://www.diabetes.org/food-nutrition-lifestyle/lifestyle-prevention/risk-test.jsp), published in 2008, was validated with findings from the Third National Health and Nutrition Survey.[10] The calculator uses answers to questions about age, waist circumference, history of gestational diabetes mellitus (GDM), height, race/ethnicity, hypertension, family history, and exercise to determine whether an individual is at high risk for undetected diabetes. The tool has a low positive predictive value (14%), but a negative predictive value >99%.[10]

The **QDScore Diabetes Risk Calculator** (www.qdscore.org), another new tool, is designed to estimate an individual's 10-year risk of developing type 2 diabetes.[11] The program, which calculates risk based on answers to questions about family history of diabetes, patient history of cardiovascular disease, smoking, treatment for hypertension, BMI, ethnicity, and steroid use, was validated with data collected from 2.5 million patients in practices throughout England and Wales. The screening tool showed a high degree of discrimination in reflecting differences in disease prevalence related to ethnic and socioeconomic risk factors.[11]

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Prediabetes increases the risk of developing type 2 diabetes by an estimated 30% over a 4-year period.

Pinning down a type 2 (or prediabetes) diagnosis

The ADA, American Association of Clinical Endocrinologists (AACE), USPSTF, and World Health Organization/International Diabetes Federation agree on the diagnostic criteria for type 2 diabetes: a fasting glucose >126 mg/dL, a random plasma glucose ≥200 mg/dL (that must be confirmed on a subsequent day), or both.[5,7,12,13] Patient history, risk factors, and additional laboratory tests can help clinicians distinguish between type 1 and type 2 diabetes.

An oral glucose tolerance test (OGTT) is also an option for diagnosis, but time and scheduling difficulties limit the routine use of this test in primary care. Hemoglobin A1c is not recommended as a diagnostic test because of a lack of standardization.[1]

Prediabetes and type 2 risk. One in 4 (25.9%) US adults 20 years of age or older and more than 1 in 3 (35.9%) of those 60 years of age or older have prediabetes,[14] defined as impaired fasting glucose (100-125 mg/dL), impaired glucose tolerance (2-hour glucose test results of 140-199 mg/dL), or both. Prediabetes increases the risk of developing type 2 diabetes by an estimated 30% over a 4-year period,[15] and 70% over 30 years,[16] although lifestyle interventions can substantially lower the risk. In a recently released consensus statement, an AACE task force noted that in addition to the increased risk of type 2 diabetes, patients with prediabetes face a greater risk of macrovascular complications.[17]

Type 2 in kids can be mistaken for type 1

As childhood obesity has surged, type 2 diabetes has been diagnosed at an increasingly early age—even in children younger than 10 years.[18] Minority youth, primarily African Americans, Hispanics, and Asians/Pacific Islanders, are at increased risk.[14] Symptoms can be insidious in children and adolescents and easily missed or mistaken for type 1 diabetes, in part because type 2 diabetes is still relatively rare in this age group.[19]

Preteens at risk. In a recent study of BMI and metabolic syndrome risk factors in 8- to 14-year-olds, however, researchers concluded that children who are overweight in early adolescence may be at risk for type 2 diabetes as well as cardiovascular disease before they reach their teens.[20] There is evidence of a genetic predisposition for type 2 diabetes and defects of β-cell function,[5,21] and family history, in addition to weight, is an important consideration in identifying type 2 diabetes in young patients.

Although young adults with type 1 and type 2 diabetes can present with similar symptoms, there may be certain clues to a type 2 diagnosis. Acanthosis ni-

TABLE

Type 1, type 2, and gestational diabetes: Diagnostic clues

	TYPE 1 DIABETES	TYPE 2 DIABETES	GESTATIONAL DIABETES MELLITUS (GDM)
Risk factors/ characteristics	Patient/family history of autoimmune disease 1st-degree relative with type 1 diabetes Normal weight with symptoms of hyperglycemia	BMI ≥25 Physical inactivity 1st-degree relative with type 2 diabetes High-risk ethnic group (African American, Hispanic, Native American, Asian American, Pacific Islander) History of GDM and/or delivery of an LGA infant BP >135/80 mm Hg or being treated for HTN Polycystic ovary syndrome IGT or IFG Acanthosis nigricans	BMI ≥30 History of GDM and/or delivery of an LGA infant (or poor outcome) 1st-degree relative with type 2 diabetes High-risk ethnic group (African American, Hispanic, Native American, Asian American, Pacific Islander) Glycosuria Age >25 years Polycystic ovary syndrome IGT
Laboratory tests/positive results	Specific antibodies to islet cell, insulin, and/or GAD* Tyrosine phosphatase-like auto antigen IA-2 (marker of autoimmune islet cell disease) C-peptide (low or absent); if in normal range, may indicate early disease and partial β-cell activity	FPG >126 mg/dL Random plasma glucose >200 mg/dL (test repeated next day) 2-hr 75-g OGTT >200 mg/dL HDL <35 mg/dL TG >250 mg/dL C-peptide (normal or elevated; may be low initially due to glucose toxicity)	Fasting: ≥95 mg/dL 1-hr OGTT: ≥180 mg/dL 2-hr OGTT: ≥155 mg/dL 3-hr OGTT: ≥140 mg/dL

BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; GAD, glutamic acid decarboxylase; HDL, high-density lipoproteins; HTN, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LGA, large for gestational age; OGTT, oral glucose tolerance test; TG, triglycerides.

*GAD65 is most specific.

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Acanthosis nigricans, which is most common in young obese patients, points to a type 2 diagnosis.

gricans, which is related to insulin resistance and occurs most frequently in obese adolescents, points to a type 2 diagnosis. Increased insulin and C-peptide levels are indicators of type 2 diabetes. Low levels are not necessarily an indication of type 1, however, because patients with type 2 diabetes may have low levels of insulin and C-peptide because of glucose toxicity and lipotoxicity at the time of diagnosis.[22] Treatment with insulin may be necessary until glucose toxicity resolves.

Type 1 diabetes: Beyond childhood

Approximately 5% to 10% of patients with diabetes have type 1, which is defined as idiopathic or cellular immune-mediated autoimmune β-cell destruction.[5] The rate of destruction is variable—it generally progresses more rapidly in infants and children than in adults. Some people with type 1 diabetes retain residual β-cell function, but have little or no insulin secretion; this manifests as a low or undetectable level of serum C-peptide.

Most cases of type 1 diabetes are diagnosed in patients younger than 18 years. But type 1 diabetes is increasingly recognized as a disorder that also develops in early adulthood, usually before the age of 40.

Arriving at a type 1 diagnosis

Patients with type 1 diabetes often present with modest hyperglycemia, but may rapidly progress to severe hyperglycemia and diabetic ketoacidosis (DKA) when infection or other physical stressors occur.

While screening for autoantibodies in asymptomatic individuals is not recommended,[5] patients with blood glucose levels ≥200 mg/dL and symptoms of polydipsia, polyuria, and polyphagia who do not meet the profile for type 2 diabetes may be candidates for additional laboratory work. Approximately 85% to 90% of patients with type 1 diabetes will have antibodies to islet cells or glutamic acid decarboxylase (GAD).[5,23]

Even without antibody testing, there are distinguishing characteristics that help support a type 1 diagnosis. As a general rule, individuals who develop type 1 diabetes—especially children—are not obese, although patients usually gain weight over time. In addition, many patients with type 1 diabetes have an autoimmune disease, such as celiac or Graves' disease, hypothyroidism, adrenal anemia, or pernicious anemia; and a first-degree relative with type 1 diabetes. DKA, with acute symptoms of polydipsia and/or polyuria and recent, unintentional weight loss, is suggestive of—but not definitive for—type 1 diabetes.

A recently validated type 1 risk calculator may be particularly useful for screening patients who have a sibling, parent, or child with type 1 diabetes. Using age, BMI, C-peptide concentration, and OGTT results, the algorithm was highly predictive of type 1 diabetes in family members of patients who tested positive for islet cell antibodies.[24]

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Although GAD or islet cell antibodies may be present in patients with LADA, insulin is usually not required at the time of diagnosis.

Patient doesn't "fit" type 1 or 2? Consider LADA

LADA, a gradual, progressive form of type 1 diabetes, can be difficult to identify. Circulating GAD or islet cell antibodies are present, but patients don't have an absolute need for insulin at the time of diagnosis. Thus, they're often thought to have type 2 diabetes.[25] Individuals with LADA show no signs of insulin resistance, however, and over time, β cells decline and insulin usually becomes necessary.

There are no universal recommendations for testing for LADA. Rather, the diagnosis should be considered in those who don't fit the classic profile for type 1 or type 2 diabetes,[26] but have some of the following features:

- age <50 years
- acute symptoms of polydipsia,

DIABETES PREVENTION PATIENT HANDOUT

Get healthier, one small step at a time

Eating well, maintaining your weight, and engaging in physical activity are essential to good health. If you have risk factors for diabetes, diet and exercise are important steps you can take to help keep the disease at bay.

Making changes to your diet and increasing the amount of exercise you engage in need not be a daunting task. It helps to remember that it's not necessary to take giant steps. You can improve your health and help prevent diabetes with a series of small changes. For best results, keep each goal small, manageable, and as specific as possible.

Eating. Do you eat fast food frequently, or snack on ice cream or potato chips when you watch TV at night? Pick a "bad habit" that is of particular concern and try to "turn it around." You might, for instance, promise yourself that:

For the next 4 weeks, I will replace my unhealthy evening snacks with fresh fruit, a small bowl of cereal, or (insert another healthy snack here).

Getting active. Have you stopped working out? Are you concerned that working out will require a big time commitment? Think again. Start small and promise yourself that:

For the next 3 weeks, I will take a 20-minute walk 3 mornings a week.

Each time you set a goal, monitor your progress. When you succeed, give yourself a reward—it can be something as simple as a long bath or a trip to the movies—and vow to continue that lifestyle change and to add another. If you aren't successful, think about why and revise your goal. If you find you're too busy getting the kids off to school to walk in the morning, for example, change your schedule and start going out during your lunch break. Or, if it's too cold or rainy, find a nearby mall where you can walk (or a treadmill at a local gym) instead. It also helps to get a step counter, or pedometer. The American Diabetes Association (ADA) recommends taking 10,000 steps per day.

For additional ideas, visit the ADA Web site (www.diabetes.org) and click on Fitness. Or call our office at _____ and make an appointment to come in and discuss additional lifestyle changes—small and large—that you can make with our help.

polyuria, and/or unintentional weight loss
- BMI <25
- a personal history of autoimmune disease
- a family history of autoimmune disease.[27]

A prospective analysis found that the majority of LADA patients had at least 2 of these distinguishing characteristics.[28] Other recent research found heterogeneity among patients with LADA. Noting that not all patients with LADA become insulin-dependent, researchers concluded that the need for insulin is linked to the degree of autoimmunity and β-cell failure.[29]

When GDM complicates prenatal care

Any degree of carbohydrate intolerance that is first recognized during pregnancy is classified as GDM, whether or not the condition resolves after delivery. A GDM diagnosis does not preclude the possibility of undiagnosed type 2 diabetes or prediabetes, or (rarely) type 1 diabetes.

Approximately 7% of all pregnancies in the United States are complicated by GDM, totaling more than 200,000 cases annually.[5] The rate of GDM is in direct proportion to the prevalence of type 2 diabetes in the population in question, and ranges from 1% to 14%.

CONTINUED

GDM is the diagnosis in nearly 90% of pregnancies complicated by diabetes.[5]

The GDM screening controversy

Screening for GDM—whether it should be done universally or selectively on the basis of risk factors—is highly controversial. The USPSTF maintains that there is insufficient evidence to recommend for or against screening women with no history of GDM. The American College of Obstetricians and Gynecologists (ACOG)[30] and ADA[5] recommend selective screening based on patient history, clinical presentation, and, possibly, prior impaired glucose test results or other abnormal laboratory values. AACE calls for universal screening of pregnant women, starting at 20 weeks for high-risk individuals and between 24 and 28 weeks for those at low risk.[12]

Identifying patients at risk. Maternal age (>25 years), obesity (BMI ≥30), prior GDM or delivery of a large-for-gestational-age infant, belonging to a high-risk ethnic group, glycosuria, history of glucose resistance or glucose tolerance, and a first-degree relative with diabetes (**TABLE**) are risk factors for GDM. Women at high risk—those who meet all or most of these criteria—should undergo early screening: at the first prenatal visit, according to ACOG;[30] upon confirmation of pregnancy (ADA);[5] at 20 weeks' gestation (AACE);[12] or between 24 and 28 weeks' gestation (USPSTF).[7] ADA and ACOG recommend a 2-stage approach, starting with a 50-g 1-hour OGTT and following up with a 100-g 3-hour OGTT if the first test results are not definitive.[5,30] Testing for patients at average risk—which includes any pregnant woman with even a single risk factor, such as being older than 25 years—should be done between 24 and 28 weeks' gestation, according to ACOG and ADA; testing is not required for women who are <25 years, have a normal body weight, and no other risk factors.

GDM screening in primary care. Because most women fit the criteria for average or high risk,[31] family physicians may find universal screening to be more practical than individual risk assessment. Universal screening is associated with favorable outcomes,[32] but screening limited to those at high and average risk also has evidence to support it. In a study of 25,118 deliveries, only 4% of women with GDM were missed by the exclusion of low-risk patients.[33]

In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, researchers tracked 25,505 women from 9 countries and found a continuous relationship between the risk of macrosomia and the rise in maternal glucose levels.[34] The impact on the developing fetus of varying degrees of glucose was studied after a 75-g 2-hour OGTT. The risk of macrosomia increased with fasting blood glucose >75 mg/dL, 1-hour glucose levels >105 mg/dL, and 2-hour glucose concentration >90 mg/dL.[35] The most compelling results for adverse effects were associated with fasting glucose levels, rather than glucose tolerance tests.

2 abnormal results needed for a GDM diagnosis

In the absence of unequivocal hyperglycemia, there are 2 diagnostic standards for GDM: The Carpenter-Coustan Conversion and the National Diabetes Data Group Conversion. The Carpenter-Coustan Conversion uses lower glucose values for fasting (≥95 mg/dL) and subsequent 1-, 2-, and 3-hour levels (≥180, 155, and 140 mg/dL, respectively) and is more widely used. But expert opinion also supports the National Diabetes Data Group Conversion criteria (fasting plasma glucose, ≥105 mg/dL; ≥190, 165, and 145 mg/dL for 1-, 2-, and 3-hour OGTT, respectively), and there are no data from clinical trials to prove the superiority of either standard.[30]

Both sets of standards require 2 or more thresholds to be met or exceeded

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Newly diagnosed patients with type 2 diabetes may require insulin until glucose toxicity resolves.

for a GDM diagnosis. Women with only 1 abnormal value should be monitored carefully, however, as they, too, may be at increased risk for macrosomia and other morbidities.[30]

Postpartum follow-up. Obtain a fasting glucose reading or perform an OGTT around the time of the postpartum checkup for any patient who was diagnosed with GDM. ACOG recommends using an OGTT to more accurately diagnose type 2 diabetes or prediabetes in these patients, who are at significantly elevated risk.[30] ■

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